REMARKS

Claims 1-15 are pending in the present application. Claims 1, 6 and 11 are amended and claim 15 is canceled without prejudice. Support for the amendment to claims 1, 6 and 11 can be found, *inter alia*, on page 4, lines 15-22 of the original specification. Specifically, the range of macrolide is between about 0.2 mg/kg/day and about 200 mg/kg/day while the range of Substance P antagonist can be between about 2 mg/kg/day and about 7 mg/kg/day, which translate into a substance P antagonist:macrolide weight ratio of between about 35:1 and about 1:100.

Therefore, the present Amendment is fully supported by the original specification and does not raise any issue of new matter. Accordingly, entry of the present Amendment is respectfully requested. Upon entry of the present Amendment, claims 1-14 will be under examination.

OBJECTION TO THE DISCLOSURE

The disclosure is objected to because page 1 of the specification allegedly fails to set forth the status of the parent applications.

Applicants have amended the objected paragraph to include the status of all parent applications. Therefore, this ground of objection is moot.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-5 and 15 stand rejected under 35 U.S.C. §112, first paragraph, enablement.

In order to expedite the prosecution of the present application, without conceding to the correctness of this rejection, Applicants have amended claim 1 and canceled claim15 without prejudice. Applicants contend that the amendments to claim 1 and the cancellation of claims 15 overcome this ground of rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 6-10 stand rejected under 35 U.S.C. §112, first paragraph, enablement. The Office Action alleged that the specification does not reasonably provide enablement for preventing emesis and that the term "preventing" encompasses the use of Substance P antagonist as a vaccine. However, the Office Action admitted that the specification is enabling for treating emesis.

Applicants respectfully point out that the term "preventing" does not include the use of Substance P antagonist as a vaccine. As shown in example 1 on page 12 of the original specification, macrolide-induced emesis in mammals can be eliminated by administering Substance P antagonist to the mammals prior to the administration of the macrolides. The term "preventing" is used to describe such processes, not vaccination. Therefore, this ground of rejection is moot. Accordingly, reconsideration and withdrawal of this rejection against claims 6-10 are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §102(b)

Claims 1, 2, 4, 5, 11, 12, 14 and 15 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hagan et al., U.S. Patent No. 5,547,964 (hereinafter "Hagan"). The Office Action states that "Hagan et al. disclose the treatment of cancer with a combination of substance P antagonist with anticancer agents such as macrolide doxorubicin."

Applicants have amended claim 1 to recite "A method of treating bacterial or protozoal infection comprising the adjunctive administration to a mammalian subject in need of such treatment of a pharmaceutically effective amount of a macrolide antibiotic and a pharmaceutically effective amount of a Substance P antagonist at a dosage of between about 2 mg/kg/day and about 7 mg/kg/day."

Under M.P.E.P. § 2131, to anticipate a claim, the reference must disclose every element of the claim. Applicants respectfully contend that Hagan does not disclose the use of "macrolide", nor does Hagan disclose the use of "a pharmaceutically effective amount of a Substance P antagonist at a dosage of between about 2 mg/kg/day and about 7 mg/kg/day." In fact, Hagan disclosed, in Column 1, the use of "doxorubicin" which is an anthracycline antibiotic having multiple ring structure (see attached Merck Index, pages 540 and 541), not a macrolide having one large ring structure.

Therefore, Hagan does not anticipate claim 1 because Hagan does not teach every element of claim 1. Hagan also does not anticipate claims 2, 4, 5 because these claims are dependent upon claim 1 and incorporate all the elements of claim 1.

With regard to claims 11, 12, 14 and 15, applicants respectfully point out that claim 15 is canceled without prejudice and claim 11 is amended to recite "A pharmaceutical composition comprising a pharmaceutically effective amount of a macrolide antibiotic, a pharmaceutically effective amount of a Substance P antagonist, and optionally, a carrier;

wherein the weight ration of said substance P antagonist and said macrolide antibiotic is between about 35:1 and about 1:100."

Hagan does not disclose the use of "macrolide" nor "a pharmaceutically effective amount of a Substance P antagonist" having a weight ratio of between about 35:1 and about 1:100 to the macrolide. Therefore, Hagan does not anticipate claim 11 under the standard of M.P.E.P. § 2131. Hagan also does not anticipate claims 12 and 14 because these claims are dependent upon claim 11 and incorporate all the elements of claim 11. Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 1-15 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Macy et al., U.S. Patent No. 5,958,888 (hereinafter "Macy") or Schadewald et al., U.S. Patent No. 5,468,735 (hereinafter "Schadewald") in combination with applicant's alleged admittance on page 1 of the specification and with Hagan.

Applicants respectfully point out that the Office Action fails to establish a *prime facie* case of obviousness under the standard of M.P.E.P. § 2142 which states that:

> to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

The Office Action does not meet at least the first and the third criteria. Specifically, Macy disclosed a water miscible macrolide antibiotic composition, Schadewald disclosed an animal feed premix composition, and page 1 of the specification which cites Hall, J.A., and Washabau, R.J., *Small Animal Gastroent.* 19(3):261-268 (1997) (hereinafter "Hall") for its statement that "macrolide antibiotics tend to cause emesis in companion animals."

Applicants respectfully point out that neither Macy nor Schadewald provide any specific teaching, suggestion or motivation to a skilled artisan on how to obtain the claimed "method of treating bacterial or protozoal infection comprising the adjunctive administration to a mammalian subject in need of such treatment of a pharmaceutically effective amount of a macrolide antibiotic at a dosage of between about 0.2 mg/kg/day and about 200 mg/kg/day

and a pharmaceutically effective amount of a Substance P antagonist at a dosage of between about 2 mg/kg/day and about 7 mg/kg/day," or "method of preventing or treating emesis associated with a macrolide antibiotic comprising administering to a subject in need of such treatment a pharmaceutically effective amount of a Substance P antagonist at a dosage of between about 2 mg/kg/day and about 7 mg/kg/day," or the claimed "pharmaceutical composition comprising a pharmaceutically effective amount of a macrolide antibiotic, a pharmaceutically effective amount of a Substance P antagonist, and optionally, a carrier; wherein the weight ratio of said substance P antagonist and said macrolide antibiotic is between about 35:1 and about 1:100." Hall and Hagan does not remedy the deficiency of Macy and Schadewald as neither Hall nor Hagan teach or suggest the use of a macrolide and substance P antagonist together at the specified dosage.

Moreover, without looking at the disclosure of the present application, one of ordinary skill in the art would not know from Macy, Schadewald, Hall and Hagan how to obtain the claimed methods and composition having the advantages described in the specification, e.g. dogs did not vomit when treated for infection using the claimed methods and/or composition. In fact, table 1 on pages 12 and 13 of the original specification shows that only the use of compound CP122,721, a substance P antagonist, completely prevented macrolide-induced dog vomiting. Page 13 of the original specification also shows that "the incidence of emesis was not reduced in dogs given 1.5 mg/kg CP122,721, but 3 mg/kg CP122,721 was completely effective in preventing azithromycin emesis." Therefore, the Office Action does not satisfy the first criteria for establishing a *prime facie* case of obviousness under M.P.E.P. § 2143.01 because the "suggestion or motivation" criteria must be satisfied from the disclosure of the prior art reference or from the knowledge of persons skilled in the art, not by the use of hindsight in view of the present application (emphasis added).

In this case, even assuming that Macy, Schadewald, Hall and Hagan can be combined, the combination does not disclose "all the claim limitations." Specifically, the combination of these references does not teach or suggest the use of a macrolide at a dosage of between about 0.2 mg/kg/day and about 200 mg/kg/day and substance P antagonist at a dosage of between about 2 mg/kg/day and about 7 mg/kg/day to treat infections without causing macrolide-induced emesis. The combination also does not teach or suggest the use of substance P antagonist and macrolide at a weight ratio of between about 35:1 and about 1:100 to treat macrolide-induced emesis. Therefore, the Office Action fails to satisfy the third criteria for establishing a *prime facie* case of obviousness under the M.P.E.P. § 2143.01.

Moreover, the foregoing illustrates that the Patent Office's rejection is an impermissible "obvious to try" rejection. As stated *In re O'Farrell*:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

7 U.S.P.Q. 2d 1673, 1681 at 1681 (Fed. Cir. 1988) (citations omitted).

It is clear that this rejection is the first of these, especially in light of the fact that "it is well known that antiemetic drugs are not equally effective in preventing or reducing emesis in different species of animals. Lucot, J.B., *et al.*, *British J. Pharmacol.* 120(1):116-120 (1997)," and "antiemetic drugs are typically effective against only one or a few emetic stimuli. For example, 5-hydroxytryptamine antagonists are only effective against vomiting elicited by ipecac, radiation, acute cancer chemotherapy and, to a lesser extent, recovery from anesthesia. Lucot, J.B., *et al.*, *British J. Pharmacol.* 120(1):116-120 (1997)."

Applicant respectfully points out that Macy, Schadewald, Hall and Hagan do not sets out all the parameters used in the present invention, let alone providing indication as to which parameter is critical and how to select among various parameters so as to arrive at the claimed methods and/or composition. However, even assuming that Macy, Schadewald, Hall and Hagan had listed all the parameters, this rejection still does not meet the standard set forth in *In re O'Farrell* by the Federal Circuit Court because it would fall within the first of these two types of errors in obviousness rejection. Therefore, claims 1-14 are nonobvious over the combination of Macy, Schadewald, Hall and Hagan as "obvious to try" rejection is not permissible under *In re O'Farrell*: 7 U.S.P.Q. 2d 1673, 1681 at 1681 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

In addition, applicants have achieved unexpected results of treating infections without causing emesis by selecting a combination of macrolide and substance P antagonist at a

particular dosage range and/or weight ratio. In one example, only the use of compound CP122,721, a substance P antagonist, completely prevented macrolide-induced dog vomiting, *see table 1 on pages 12 and 13 of the original specification.* In another example, the incidence of emesis was not reduced in dogs given 1.5 mg/kg CP122,721, but 3 mg/kg CP122,721 was completely effective in preventing azithromycin emesis, *see Page 13 of the original specification.* Therefore, the claimed methods are nonobvious over the disclosure of Macy, Schadewald, Hall and Hagan as "superiority of a property shared with the prior art is evidence of nonobviousness," M.P.E.P. § 716.02 (a). Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

CONCLUSION

In view of the claim amendments and the remarks, further and favorable considerations of the presently pending claims are respectfully requested.

It is believed that no fee is required for the consideration of this Amendment. However, if any fees are required, the Commissioner is authorized to charge such fees to our Deposit Account No. 16-1445.

DATE: OCT. 6, 2004

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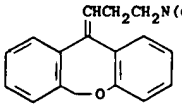
mol wt 279.37. C 81.68%, H 7.58%, N 5.01%, O 5.73%. Prepn of mixture of *cis*- and *trans*-isomers: K. Stach, F. Bickelhaupt, *Monatsh.* **93,** 896 (1962); F. Bickelhaupt *et al., ibid.* **95,** 485 (1964); **Neth. pat. Appl. 6,407,758;** K. Stach, **U.S. pat. 3,438,981** (1965, 1969 both to Boehringer Mann.); and separation and activity of isomers: B. M. Bloom, J. R. Tretter, **Belg. pat. 641,498;** *eidem,* **U.S. pat. 3,420,851** (1964, 1969 both to Pfizer). Pharmacology: A. Ribbentrop, W. Schaumann, *Arzneimittel-Forsch.* **15,** 863 (1965). Metabolism in animals: D. C. Hobbs, *Biochem. Pharmacol.* **18,** 1941 (1969). Determn in plasma by GC/MS: T. P. Davis *et al., J. Chromatog.* **273,** 436 (1983); by HPLC: T. Emm, L. J. Lesko, *ibid.* **419,** 445 (1987). Clinical study in depression: K. Rickels *et al., Arch. Gen. Psychiat.* **42,** 134 (1985). Comparative clinical trial with cimetidine, *q.v.,* in treatment of ulcer: R. K. Shrivastava *et al., Clin. Ther.* **7,** 181 (1985). Review of pharmacology and therapeutic efficacy: R. M. Pinder *et al., Drugs* **13,** 161 (1977).



Oily liq consisting of a mixture of *cis*- and *trans*-isomers. $bp_{0.03}$ 154-157°, $bp_{0.2}$ 260-270°. LD_{50} in mice, rats (mg/kg): 26, 16 i.v.; 79, 182 i.p.; 135, 147 orally (Ribbentrop, Schaumann).

Hydrochloride, $C_{19}H_{22}ClNO$, ***Adapin, Aponal, Curatin, Novoxapin, Quitaxon, Sinequan.*** Crystals, mp 184-186°, 188-189°. (A *cis-trans* mixture of approx 1:5).

Maleate, crystals, mp 161-164°, 168-169°.

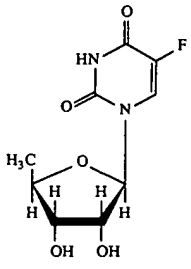
trans-Form hydrochloride, mp 192-193°.

cis-Form hydrochloride, ***P-4599, cidoxepin.*** Crystals, mp 209-210°.5.

THERAP CAT: Antidepressant.

THERAP CAT (VET): Antipruritic.

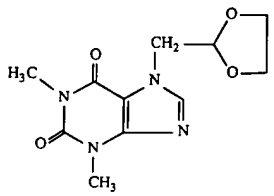
3426. Doxifluridine. *5'-Deoxy-5-fluorouridine;* 1-(β-D-5'-deoxyribofuranosyl)-5-fluorouracil; 5'-DFUR; 5'-dFUrd; Ro 21-9738; Flutron; Furtulon. $C_9H_{11}FN_2O_5$; mol wt 246.20. C 43.91%, H 4.50%, F 7.72%, N 11.38%, O 32.49%. Fluorinated pyrimidine nucleoside with cytostatic activity. Prepn: A. F. Cook, **U.S. pat. 4,071,680** (1978 to Hoffmann-La Roche); H. Hrebabecky, J. Beranek, *Nucleic Acids Res.* **5,** 1029 (1978); A. F. Cook *et al., J. Med. Chem.* **22,** 1330 (1979). Stereospecific synthesis: J. Kiss *et al., Helv. Chim. Acta* **65,** 1522 (1982). Mechanism of action studies: H.-R. Hartmann, A. Matter, *Cancer Res.* **42,** 2412 (1982); R. D. Armstrong *et al., Cancer Chemother. Pharmacol.* **11,** 102 (1983). Kinetics and metabolism in humans: J.-P. Sommadossi *et al., Cancer Res.* **43,** 930 (1983). Clinical trials in colorectal carcinoma: R. Abele *et al., J. Clin. Oncol.* **1,** 750 (1983); S. D. Fossa *et al., Cancer Chemother. Pharmacol.* **15,** 161 (1985). Series of articles on animal toxicology: *Yakuri to Chiryo* **13,** Suppl. 2, 221-430 (1985); acute toxicity: M. Shimizu *et al., ibid.* 209, *C.A.* **104,** 14673z-14678e (1986). Evaluation of neurotoxicity in humans: M. S. Heier, S. D. Fossa, *Acta Neurol. Scand.* **73,** 449 (1986).



Crystals from ethyl acetate, mp 189-190° (Cook). Also reported as crystals from 2-propanol, mp 186-188° (Hrebabecky, Beranek); needles from methanol + ethyl acetate, mp 192-193° (Kiss). pKa 7.4. $[\alpha]_D^{25}$ +18.4° (c = 0.419 in water). uv max (in methanol): 268-269 nm (ε 8550). LD_{50} (14 day) in mice or rats (mg/kg): > 1000 i.v.: > 2000 [illegible] male, female mice, male, female rats (mg/kg): > [illegible] > 5000, 3471, 3390 orally (Shimizu).

THERAP CAT: Antineoplastic.

3427. Doxofylline. *7-(1,3-Dioxolan-2-ylmethyl)-1[illegible]hydro-1,3-dimethyl-1H-purine-2,6-dione; 7-(1,3-dioxolan-2-ylmethyl)theophylline;* 2-(7'-theophyllinemethyl)-1,[illegible] oxolane; doxophylline; dioxyfilline; ABC 12/3; An[illegible] Ventax. $C_{11}H_{14}N_4O_4$; mol wt 266.26. C 49.62%, H 5.30%, 21.04%, O 24.04%. Prepn: U. Avico *et al., Farmaco Ed.* **17,** 73 (1962). Use as bronchodilator: **Belg. pat. 868,[illegible]** S. Franzone, T. Tamietto, **U.S. pat. 4,187,308** (1978, [illegible] Istituto Biologico Chemioterapico ABC). Pharmacology: S. Franzone *et al., Farmaco Ed. Sci.* **36,** 201 (1981). [illegible] macodynamics and toxicity in rats: J. S. Franzone *et al., ibid.* 220. HPLC determn in pharmaceutical compounds: C. Badini *et al., Farmaco Ed. Prat.* **37,** 320 (1982). Clinical trial in obstructive pneumopathy: C. Bucca *et al., Int. J. Clin. Pharm. Res.* **11,** Suppl 1, 101 (1982).

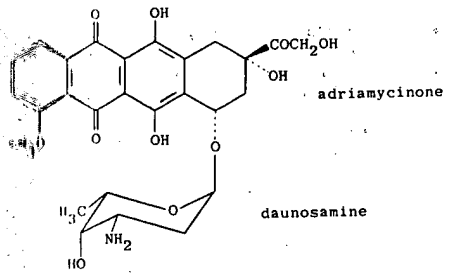


Crystals, mp 144-145.5°. Sol in water, acetone, ethyl [illegible] tate, benzene, chloroform, dioxane, hot methanol or [illegible] ethanol. Practically insol in ethyl ether or petr ether. [illegible] in mice (mg/kg): 841 orally; 215.6 i.v.; in rats: 1022.4 [illegible] ly, 445 i.p. (Franzone).

THERAP CAT: Bronchodilator.

3428. Doxorubicin. *(8S-cis)-10-[(3-Amino-2,3,[illegible] deoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrah[illegible] 6, 8, 11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,[illegible] naphthacenedione;* 14-hydroxydaunomycin; NSC-[illegible] FI 106. $C_{27}H_{29}NO_{11}$; mol wt 543.54. C 59.66%, H 5.[illegible] 2.57%, O 32.38%. Anthracycline antibiotic isolated [illegible] *Streptomyces peucetius* var *caesius:* F. Arcamone *et al.,* **Afr. pat. 68 02378** and **U.S. pat. 3,590,028** (1968 and [illegible] to Farmitalia); *eidem, Biotechnol. Bioeng.* **11,** 1101 ([illegible] Synthesis of derivs: F. Arcamone *et al.,* **Ger. pat. 1,9[illegible]** (1969 to Farmitalia), *C.A.* **73,** 45799r (1970). Stru[illegible] studies: F. Arcamone *et al., Tetrahedron Letters* **1969,** [illegible] Synthesis from daunomycin, *q.v.: eidem, Chim. Ind. (*[illegible] **51,** 834 (1969); *see also:* E. M. Acton *et al., J. Med. C*[illegible] **17,** 659 (1974); from 7-deoxydaunomycinone: T. H. [illegible] *et al.,* **U.S. pat. 4,012,448** (1977 to Stanford Res. [illegible] Biochemical comparison with daunomycin: Wang [illegible] *Proc. Am. Assoc. Cancer Res.* **12,** No. 62, 77 (1971). In [illegible] environment doxorubicin breaks up into a water-insol[illegible] aglycone, *adriamycinone* ($C_{21}H_{18}O_9$), and a water-sol[illegible] reducing aminosugar, *daunosamine* ($C_6H_{13}NO_3$), 3-[illegible] 2,3,6-trideoxy-L-lyxohexose: A. Di Marco *et al., Tumori Chemother. Rep.* (part 1) **53,** 33 (1969). Total synthesis of adriamycinone: F. Suzuki *et al., J. Am. Chem. Soc.* **[illegible]** 2272 (1978); regiospecific synthesis: J. S. Swenton, [illegible] Reynolds, *ibid.* 6188; of daunosamine: P. M. Wovkulich, [illegible] R. Uskonovic, *Tetrahedron* **41,** 3455 (1985). Pharmacokinetic and chemotherapeutic studies: E. Arena *et al., Arzneimittel-Forsch.* **21,** 1258 (1971). Purification: E. Oppici, **Belg. pat. 898,506;** *eidem,* **Brit. pat. Appl. 2,133,003** (1984 to Farmitalia). As modulator of immune response: E. Mihich, M. J. Ehrke, *Transplant. Proc.* [illegible] (1984). Doxorubicin's cytotoxicity appears to be due to [illegible] ability to intercalate with DNA, interact with [illegible] membranes and take part in oxidation-reduction reactions: T. R. Tritton, G. Yee, *Science* **217,** 248 (1982); H. [illegible] *et al., Cancer Res.* **44,** 613 (1984); R. S. Youngman [illegible] Elstner, *Arch. Biochem. Biophys.* **231,** 424 (1984). In treatment of cancer of the bladder: M. Pavone-Macaluso [illegible] *Urology* **23,** 40 (1984); breast: D. C. Tormey *et al.,* [illegible]

...1, 231 (1984); prostate: H. Scher *et al., J. Urol.* ... (1984). Toxicology: C. Bertazzoli *et al., Experi-* ... (1970); *eidem, Toxicol. Appl. Pharmacol.* **21,** ... H, D. Olson *et al., Life Sci.* **29,** 1393 (1981). ... properties, biosynthesis, fermentation: R. J. ... M, Stroshane, *Drugs Pharm. Sci.* **22,** 569-594 ... efficacy: H. L. Davis, T. E. Davis, *Cancer Treat.* ... 815 (1979). *Review:* R. H. Blum, S. K. Carter, *Ann. Med.* **80,** 249-259 (1974); G. Aubel-Sadron, D. ... Gualtieri, *Biochimie* **66,** 333-352 (1984). Compre- ... description: A. Vigevani, M. J. Williamson in *Ana-* ... *Profiles of Drug Substances* **vol. 9,** K. Florey, Ed. ... Press, New York, 1980) pp 245-274. Book: ... P. Arcamone, Ed. (Academic Press, New York, ... pp.



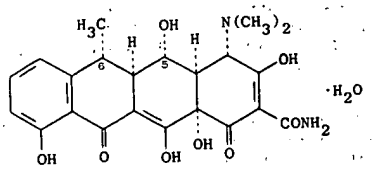
... 229-231°.

...hydrochloride, $C_{27}H_{30}ClNO_{11}$, ***Adriacin, Adriblastina,*** ...*mycin.* Orange-red colored thin needles, mp 204-205° ... $[\alpha]_D^{20}$ +248° (c = 0.1 in methanol). Absorption max ...nol): 233, 252, 288, 479, 496, 529 nm. Sol in water, ...nol, aq alcohols. Practically insol in acetone, benzene, ...form, ethyl ether and petroleum ether. Aq solns are ...orange at acid pHs, orange-red at neutral pHs and ...blue at pH >9. Aq soln unchanged after one month ... but unstable at higher temperatures or at either acid or ...line pHs. LD_{50} i.v. in mice: 21.1 mg/kg (Bertazzoli, ...).

Note: This substance may reasonably be anticipated to be ...gen: *Fourth Annual Report on Carcinogens* (NTP ...1985) p 17.

THERAP CAT: Antineoplastic.

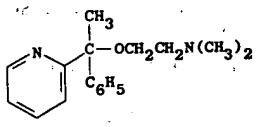
3429. Doxycycline. *4-(Dimethylamino)-1,4,4a,5,5a,6,-...octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-...dioxo-2-naphthacenecarboxamide monohydrate;* α-6-...-5-hydroxytetracycline monohydrate; α-6-deoxyoxy-...cycline monohydrate; 5-hydroxy-α-6-deoxytetracycline ...hydrate; GS-3065; Azudoxat; Doxitard; Doxy-Puren; ...in; Liviatin; Nordox; Spanor; Vibramycin; Vibravenös. ...$N_2O_8 \cdot H_2O$; mol wt 462.46. C 57.14%, H 5.67%, N ..., O 31.14%. Prepn of 6-deoxytetracyclines: Wittenau ...*J. Am. Chem. Soc.* **84,** 2645 (1962); Stephens *et al.,* ... **85,** 2643 (1963); Blackwood *et al.,* U.S. pat. **3,200,149** ...to Pfizer). Biological properties: English, *Proc. Soc. ...Biol. Med.* **122,** 1107 (1966). Pharmacology: Fabre, ...*therapia* **11,** 73 (1966); Gibaldi, *ibid.* **12,** 265 (1967). ...separation and configuration of 6α- and 6β-epimers: ...nau *et al., J. Am. Chem. Soc.* **84,** 2645 (1962); Stephens ...*et al., ibid.* **85,** 2643 (1963). ^{1}H-NMR study: Wittenau, ...kwood, *J. Org. Chem.* **31,** 613 (1966). Toxicity of hy-...chloride: Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 ...), Clinical trial in prophylaxis of leptospirosis: E. T. ...aji *et al., N. Engl. J. Med.* **310,** 497 (1984). *Review:* ...wards in *Pharmacological and Biochemical Properties of ...Substances* **vol. 2,** M. E. Goldberg, Ed. (Am. Pharm. ..., Washington, DC, 1979) pp 305-332.



Hydrochloride, $C_{22}H_{25}ClN_2O_8$, ***doxycycline hyclate, Diocimex, Doryx, Doxatet, Doxigalumicina, Doxy-II (caps), Doxylar, Doxy-Tablinen, Doxytem, duradoxal, Ecodox, Granudoxy, Hydramycin, Liomycin, Mespafin, Midoxin, Nivocilin, Novadox, Retens, Roximycin, Samecin, Sigadoxin, Tanamicin, Tecacin, Tetradox, Vibradox, Vibramycin Hyclate, Vibra-Tabs, Zadorin.*** Light yellow powder which crystallizes from ethanol + HCl as the hemihydrate hemialcoholate. Chars without melting at about 201°. $[\alpha]_D^{25}$ −110° (c = 1 in 0.01*N* methanolic HCl). uv max (0.01*N* methanolic HCl): 267, 351 nm (log ε 4.24, 4.12). Sol in water. The alcohol and water of crystallization are lost by drying at 100° under reduced pressure. More active biologically than the corresponding 6β-epimer hydrochloride, Wittenau *et al., loc. cit.* LD_{50} i.p. in rats: 262 mg/kg (Goldenthal).

THERAP CAT: Antibacterial.

3430. Doxylamine. *N,N-Dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine; 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]pyridine;* phenyl-2-pyridylmethyl-β-*N,N*-dimethylaminoethyl ether; 2-dimethylaminoethoxyphenylmethyl-2-picoline. $C_{17}H_{22}N_2O$; mol wt 270.38. C 75.52%, H 8.20%, N 10.36%, O 5.92%. Prepd from phenyl-2-pyridylmethylcarbinol and β-*N,N*-dimethylaminoethyl chloride in the presence of sodamide in xylene: Sperber *et al., J. Am. Chem. Soc.* **71,** 887 (1949). GC determn: H. C. Thompson *et al., J. Chromatog. Sci.* **20,** 373 (1982). Pharmacology, antihistaminic activity: B. B. Brown, H. Werner, *J. Lab. Clin. Med.* **33,** 325 (1948). Hypnotic efficacy: F. Sjöqvist, L. Lasagna, *Clin. Pharmacol. Ther.* **8,** 48 (1967). *Review:* T. J. Haley, *Dangerous Prop. Ind. Mater. Rep.* **2,** 17 (1982).



Liquid, $bp_{0.5}$ 137-141°. Sol in acids. Slightly volatile, darkens on exposure to light.

Succinate, $C_{21}H_{28}N_2O_5$, ***mereprine, Alsadorm, Decapryn succinate, Gittalun, Hoggar N, Sedaplus, Unisom.*** Crystals, mp 100-104°, sol in water. One gram dissolves in 1 ml water, 2 ml alcohol, 2 ml chloroform. Slightly sol in benzene and ether. pH (1% aq soln): 4.9 to 5.1. LD_{50} in mice, rabbits (mg/kg): 470, 250 orally; 62, 49 i.v.; in mice, male rats, female rats (mg/kg): 460, 440, 445 s.c. (Brown, Werner).

Note: A combination with pyridoxine hydrochloride, *q.v.*, has been marketed as ***Bendectin*** for nausea of pregnancy. Prior to 1976, Bendectin also contained dicyclomine, *q.v.* Discussion of Bendectin and the issue of teratogenicity: J. F. Cordero *et al., J. Am. Med. Assoc.* **245,** 2307 (1981); corr. *ibid.* **247,** 2234 (1982); L. B. Holmes, *Teratology* **27,** 277 (1983); L. J. Sheffield, R. Batagol, *Med. J. Aust.* **143,** 143 (1985).

THERAP CAT: Antihistaminic. Hypnotic.

THERAP CAT (VET): Antihistaminic.

3431. Dragon's Blood. A resinous secretion found on the fruits of *Daemonorops propinquus* Becc., *D. draco* Blume, and probably other species of *Daemonorops, Palmae* (Rattan palms). *Habit.* Sumatra, Borneo, India. *Constit.* About 55% of a red resin contg about 12-15% of bright-yellow, amorphous dracoresene; 2-3% white amorphous dracoalban. Isoln of the main coloring matter, dracorubin: Brockmann, Haase, *Ber.* **69,** 1950 (1936). Chemical studies of resin pigments: Olaniyi *et al., J. Chem. Soc. Perkin Trans. I* **1973,** 179.

Red sticks, pieces, or cakes; vitreous fracture; makes a bright-crimson powder; odorless and almost tasteless. mp at about 120° with sublimation of some benzoic acid. Insol in water; sol in alcohol.

USE: For coloring lacquers and varnishes; occasionally for coloring plasters; in photoengraving on zinc to protect metal parts against etching.

3432. Drazoxolon. *3-Methyl-4-[(2-chlorophenyl)hydrazone]-4,5-isoxazoledione;* 4-(2-chlorophenylhydrazono)-3-methyl-5(4*H*)-isoxazolone; 3-methyl-4-(*o*-chlorophenylhydrazono)-5-isoxazolone; PP 781; Ganocide; Mil-Col; Saisan.